Nuclear analogs of β-lactam antibiotics. XVII.[1] Stereospecific synthesis of penem and carbapenem precursors

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The transformation of methyl 6-α-bromopenicillanate (**6**) to *N*-methoxalyl-(3*S*)-bromo-(4*R*)-chloro-2-azetidinone (**8**) is described. Azetidinone **8** was converted, in a stereoselective manner, to (3*S*)-bromo-(4*R*)-tritylthio-2-azetidinone (**9**). Subsequent reduction of the 4-bromo substituent with zinc afforded the chiral (4*R*)-tritylthio-2-azetidinone (**10**), a useful intermediate for the synthesis of penems. Azetidinone **8** was also converted to the reactive (3*S*)-bromo-(4*R*)-chloro-2-azetidinone (**11**). Treatment of the (4*R*)-chloroderivative **11** with *n*-butyl or allylcuprate afforded the (4*R*)-butyl and (4*R*)-allylazetidinones **12** and **13** as the predominant diastereomers. Finally, an improved synthesis of **11** to **13** using tetraallyltin is also described.

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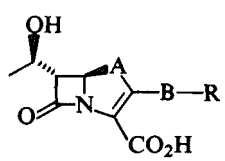
On décrit la transformation de l'α-bromo-6 pénicillanate de méthyle (**6**) en *N*-méthoxalyl-bromo (3*S*) chloro (4*R*) azétidinone-2 (**8**). On transforme l'azétidinone (**8**) d'une façon stéréosélective en bromo (3*S*) tritylthio (4*R*) azétidinone-2 (**9**). La réduction subséquente du brome en position 4, par le zinc, permet d'obtenir le composé chiral: la tritylthio (4*R*) azétidinone-2 (**10**), un intermédiaire utile pour la synthèse des pénems. On a également transformé l'azétidinone (**8**) en bromo (3*S*) chloro (4*R*) azétidinone-2 (**11**). La réaction du dérivé chloré (4*R*) (**11**) avec le *n*-butyle ou l'allylcuprate donne les butyles (4*R*) et les allyl (4*R*) azétidinones **12** et **13** comme diastéréoisomères majoritaires. On décrit également une synthèse améliorée des composés **11** à **13** qui fait appel au tétraallylétain.

[Traduit par le journal]

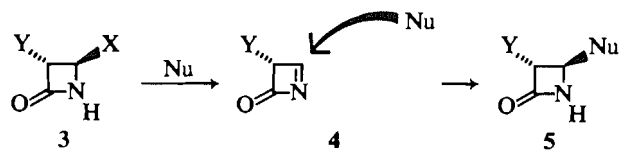
The discovery of thienamycin (**1**) (2) and the subsequent disclosure of the penem system (**2**) by Woodward (3) opened new synthetic challenges to organic chemists. The accessibility to both nuclei via a common chiral intermediate became highly desirable in terms of synthetic strategy. An enormous amount of work has already been documented for the manipulation and transformation of penicillins to various azetidinone nuclei (for a recent review, see ref. 4). The pioneering work of Kukolja (5) on the chlorinolysis of penicillins and the subsequent work by Wolfe *et al.* (6) and Sheehan *et al.* (7) first demonstrated the potential of a 3-substituted 4-chloro-2-azetidinone. The penicillin nucleus, because of its low cost and chirality, remains the substrate of choice for degradation to a precursor giving access to both chiral penems (8) and carbapenems.

Our approach was based on the conversion of a penicillin to a chiral azetidinone derivative, such as **3**, having (a) a leaving group (X) at position 4 and (b) a 3-α substituent (Y) that would be bulky enough to induce a stereoselective β-face entry of the incoming nucleophile (Scheme 1).



1, A = CH_2, B = S
2, A = S, B = CH_2

We found that the α-bromine substituent in the readily available methyl 6-α-bromopenicillanate (**6**) (9) was indeed capable of inducing complete chiralty when SNi displacement reactions (10) were performed at the adjacent position. Consequently we now report (1) the transformation of **6** to *N*-methoxalyl-(3*S*)-bromo-(4*R*)-chloro-2-azetidinone (**8**) and (3*S*)-bromo-(4*R*)-chloro-2-azetidinone (**11**), (2) the conversion of **8** or **11** to (4*R*)-tritylthio-2-azetidinone (**10**), and (3) the synthesis of (3*S*)-bromo-(4*R*)-allyl-2-azetidinone (**13**) from **11**.



SCHEME I

Treatment of methyl 6-α-bromopenicillanate (**6**) (obtained in 93% yield from the corresponding acid (MeI, DMF)) with chlorine (2.6 equiv., CH_2Cl_2) at low temperature gave the *trans* 4-chloroazetidinone **7**[5] in excellent yield (86%). The ^{1}Hmr spectrum of derivative **7** (see Table 1) showed, for H-3 and H-4 respectively, two doublets centered at 4.90 and 5.84 with a small coupling constant (ref. 11) ($J_{3,4}$ = 1.0 Hz). Interestingly, the corresponding *cis* isomer was not observed in the reaction mixture. Ozonolysis of methyl α-[(3*S*)-bromo-(4*R*)-chloro-2-azetidinon-1-yl]-β-methylcrotonate (**7**) (12) in CH_2Cl_2 (−78°C) with subsequent reduction of the ozonide with $(CH_3)_2S$ (13) gave, after careful work-up, the labile *N*-methoxalyl derivative **8** (yield 94%). Azetidinone **8** revealed a carbonyl absorption at remarkably high frequency in the infrared (ν_{max} (CH_2Cl_2): 1840 (s), 1805 (sh), 1760 (s), and 1730 (s) cm^{-1}).

When treated with 2,4-dinitrophenylhydrazine (THF, room temperature, 18 h) compound **8** gave the labile (3*S*)-bromo-(4*R*)-chloro-2-azetidinone **11** (yield 71%) that could be isolated from the reaction residue by extraction and crystallization from hexane. Although unstable at room temperature in the presence of moisture, the crystalline[6] **11** could be kept in an

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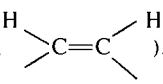
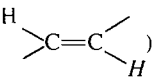
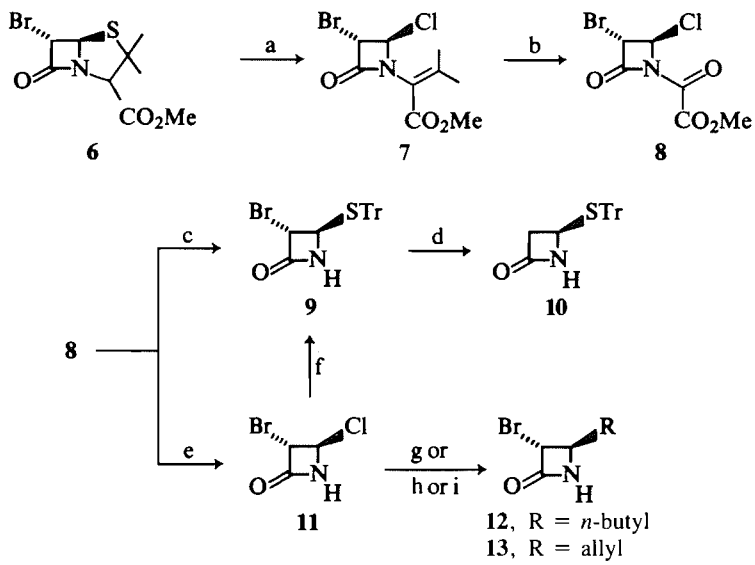
[5]Satisfactory analytical data were obtained for all new compounds.
[6]Since decomposition of **11** occurred upon heating, no melting point was observed.

TABLE 1. ^{1}H magnetic resonance spectral data*

Compound	H-3	H-4	Others
7	4.90 (d) J = 1.0	5.84 (d) J = 1.0	3.79 (s, 3H, OCH_3), 2.31 (s, 3H, CH_3) 2.02 (s, 3H, CH_3)
8	4.99 (d) J = 1.7	5.94 (d) J = 1.7	3.98 (s, 3H, OCH_3)
9	4.64 (t) J = 2.0	4.50 (d) J = 2.0	7.49–7.25 (m, 15H, aromatic-H) 4.9 (bs, 1H, NH)
10	3.28, 2.83 (dd) J = 15 J = 15 J = 5.2 J = 2.9 J = 2.0 J = 1.5	4.43 (dd) J = 5.2 J = 2.9	7.55–7.15 (m, 15H, aromatic-H) 6.9 (bs, 1H, NH)
11	4.90 (dd) J = 1.0 J = 2.5	5.62 (d) J = 1.0	6.44 (bs, 1H, NH)
12	4.37 (dd) J = 1.9 J = 2.2	3.75 (dt) J = 1.9 J = 6.6	6.12 (bs, 1H, NH), 1.83–1.26 (m, 6H, CH_2) 0.93 (t, 3H, CH_3)
13	4.42 (t) J = 2.1	3.89 (dt) J = 1.8 J = 6.6	6.05 (bs, 1H, NH), 6.06–5.55 (m, 1H, CH_2—CH=), 5.29–5.23 (m, 1H, ), 5.16–5.04 (m, 1H, ) 2.54–2.36 (m, 2H, CH_2)

*Recorded at 80 MHz in $CDCl_3$ using tetramethylsilane as internal standard. The chemical shifts are recorded in δ (ppm) and the J's in Hz.



(a) Cl_2, CH_2Cl_2, −78° to 0°C, 1h; (b) O_3, CH_2Cl_2, −78°C, $(CH_3)_2S$; (c) TrSNa, MeOH, −15°C, 30 min; (d) Zn, MeOH, CH_3CO_2H, −15°C, 20 min; (e) 2,4-dinitrophenylhydrazine, THF, 18 h, 20°C; (f) TrSNa, i-PrOH/H_2O, 3:1, 0°C, 30 min; (g) Li Cu(n-butyl)$_2$, ether, THF, −78° to −40°C, 1.25 h; (h) Li Cu(CH_2CH=CH_2)$_2$, THF, ether, −78°C, 20 min; (i) Sn(CH_2CH=CH_2)$_4$, CH_2Cl_2 or THF, −78° to 20°C, 3.5 h.

SCHEME 2

air-tight container at low temperature (Dry Ice) for months without serious degradation.

Addition of azetidinone **11** to a solution of sodium triphenylmethyl mercaptide (1.5 equiv.) in isopropanol–water gave the chiral *trans* azetidinone **9** ($J_{3,4}$ = 2 Hz, mp 130–131°C, $[\alpha]_D^{25}$ +48.2° (c 0.305, MeOH)) in 25% yield. As observed for 4-acetoxazetidinone (10) and other *N*-unsubstituted azetidinones (14a), conversion of **11** to **9** presumably proceeds

through intermediate **4** (Y = Br). None of the possible *cis*-diastereomers of **9** could be detected in the reaction mixture, which indicated the high stereocontrol (10, 14) exerted by the 3-α-bromine atom on the nucleophilic attack at position 4. Removal of bromine with zinc in methanol afforded the pure (4*R*)-tritylthio-2-azetidinone (**10**) (mp 119−119.5°C, $[\alpha]_D^{25}$ +70.5° (*c* 0.112, MeOH)) in 76% yield. Racemic **10** has already been described as a key intermediate in the synthesis of 6-unsubstituted and substituted penems (8, 15).

Alternatively, the azetidinone **9** could be obtained in one step from **8** by using an excess (2 equiv., MeOH) of triphenylmethyl mercaptide. Presumably the nucleophile first cleaved the *N*-methoxalyl group to liberate **11** *in situ*, which then reacted with a second molecule of the nucleophile as described above. Thus addition of **8** to sodium triphenylmethyl mercaptide gave, after filtration on silica gel, the desired azetidinone **9** (yield 49%) which was identical with the sample described above.

Onoue *et al.* (16) have reported the coupling of allylcopper with *N*-substituted 4-chloroazetidinone to give mixtures of the corresponding 4-α and 4-β-allylazetidinones. Due to the facile formation of reactive intermediates such as **4**, *N*-unsubstituted azetidinones usually undergo nucleophilic substitution at position 4 more readily than their *N*-substituted counterparts. Accordingly, the coupling of cuprates with azetidinone **11** was attempted. Treatment of **11** with lithium di-*n*-butylcuprate (17) gave a 57% yield of the corresponding (4*R*)-*n*-butyl-(3*S*)-bromo-2-azetidinone (**12**, $J_{3,4}$ = 1.9 Hz).

Since 4-allylazetidinones have been reported as useful intermediates for carbapenems (16, 18), the coupling of lithium diallylcuprate (generated from tetraallyltin or triphenylallyltin) (19) with azetidinone **11** was carried out. In this way a good yield (75%) of the allylazetidinone **13** was obtained, with the desired *trans* diastereomer as the major component (95:5, *trans*/*cis*, estimated by ^{1}Hmr). The pure *trans* isomer **13** ($J_{3,4}$ = 1.8 Hz $[\alpha]_D^{25}$ +38.6° (*c* 0.78, MeOH)) could be isolated by column chromatography (silica gel, 2−8% ether/CH_2Cl_2). Since tin derivatives are reported to react with acid chlorides (20), it was speculated that azetidinone **11**, via **4** (Y = Br), might react with tetraallyltin directly. Indeed, treatment of **11** with tetraallyltin in CH_2Cl_2 also gave a high yield (86%) of **13** as a mixture of *trans* (82%) and *cis* (18%) diastereomers.[7] This reaction was also found to be solvent dependent, with the ratio being greatly improved in favor of the *trans* isomer **13** (*trans*/*cis*, 92.5:7.5)[7] when THF was used as solvent. To our knowledge, this is the first report of a C4—C azetidinone coupling reaction of this type.

In summary, (3*S*)-bromo-(4*R*)-chloro-2-azetidinone (**11**) was prepared in high overall yield (53%) from 6-α-bromopenicillanic acid. Azetidinones **11** and **8** are key intermediates for the preparation of chiral penem and carbapenem precursors (**10**, **13**). The preparation of allylazetidinone **13** was greatly improved by using tetraallyltin instead of allylcuprate.

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[7]Determined by hplc on a Waters Associates PrePak-500 silica column.

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